

INITIATOR TRIGONOX R-938

STATEMENT
TOXICOKINETIC ASSESSMENT OF
INITIATOR [REDACTED]

Author:

[REDACTED]

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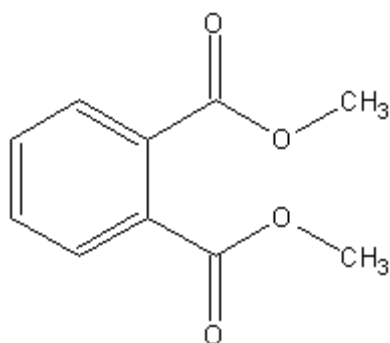
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SUMMARY OF NOTIFICATION DOSSIER ON INITIATOR [REDACTED]

1. Composition

INITIATOR [REDACTED] is colourless liquid. Technically, It is a mixture of mon- peroxidic compounds, mostly mono- and dimers of [REDACTED] dissolved in dimethylphthalate.



The molecular formula of the main component, dimethylphthalate or DMP (dimethyl 1,2-benzene dicarboxylate)

The molecular formula is $C_{10}H_{10}O_4$, its molecular weight is 194.19.

Impurities:

Above named MIPKP type III is listed as an impurity in the notification, since the concentration is below 10% . Minor impurities include isopropylketone (3-methyl-2-butanone), water and hydrogen peroxide.

2. Physical chemistry:

		Notox report nr.
Freezing temperature	$\leq -50^{\circ}$	111834
boiling point	$> 80^{\circ} \text{ C at } 101.3 \text{ Kpa}$	338568
Vapour pressure	761 Pa at 20° C^1	338581
Surface tension	52.6 mN/m at 20° C	338581
Water solubility	Unstable in water	3540848
	DMP: ~4 gr/l	338603
	[REDACTED]	"
	[REDACTED]	"
	[REDACTED]	"
	[REDACTED]	"
Partition coefficient (Log Pow)	DMP: 1.6 other components: 0.27 - 3.4.	338614
Particle size	Not applicable	

3. TOXICOKINETIC ASSESSMENT OF INITIATOR [REDACTED].

Overview of toxicity

Toxicological properties:		
Acute oral toxicity	$200 < \text{LD}_{50} < 2000$	327331
Acute dermal toxicity	$\text{LD}_{50} < 2000 \text{ mg/kg}$	338671
28 days subacute toxicity	NOAEL ca. 15 mg/kg/d	338671

The acute oral toxicity of INITIATOR [REDACTED] is moderately high, with the LD_{50} between 200 and 2000 mg/kg. The acute dermal toxicity is low, with an $\text{LD}_{50} > 2000 \text{ mg/kg}$, albeit with severe and permanent local damage.

The 28-day toxicity study revealed that [REDACTED] has an NOAEL of 15 mg/kg, with effects on the liver as the main observation at the next-higher (and top) dose level of 75 mg/kg (references in table above)

Below, an assessment of the anticipated toxicokinetic behaviour of INITIATOR [REDACTED] is given. A separation has been made between the phlegmatizer DMP on the one hand, since this is a reasonably well documented "existing substance" and the new organic peroxides on the other.

A. Dimethylphthalate

Dimethylphthalate (DMP) belongs to the class of alkyl phthalates. DMP (CAS 131-11-3) has an EINECS number (206-01106), has been used as an insect repellent (dermal application) and as a plasticiser in various plastics, among them medical appliances.

toxicity of DMP:

DMP is of relatively low toxicity, with an oral $\text{LD}_{50} > 5000 \text{ mg/kg}$ (1) and a dermal LD_{50} , rabbit > 12.000 (2). An LC_{50} is not known, probably because of its very low vapour pressure (see below, inhalatory exposure). An LC_{50} of $> 9600 \text{ mg/m}^3 / 6\text{hrs}$ in the cat has been

¹ based on the structural formulae a lower vapour pressure was expected. the relatively high value was probably due the presence of water and 3-methyl-2-butanone

reported(3), presumably with heated vapour or an aerosol. The toxic effects of the mixture are most likely not due to DSM. Available literature data indicate that the long-term effects of DMP are not very pronounced. Contrary to phthalates with longer and branched alkyl chains, DMP has no effects on reproduction or hormonomimetic effects (4,5,6,7). DMF has no promotor effects on skin tumours in mice (8)

Absorption of DMP:

Based on the log Pow of 1.6 (Notox report 338614) and data from the analogue diethylphthalate (7), DMP can be expected to be absorbed through the skin. This is also confirmed by literature data indicating that 20-40% of DMP will pass the intact rat skin (9). Based on the log Pow and water solubility, DMP can be expected to be absorbed from the gastro-intestinal tract. This is confirmed by data from the literature describing the distribution after oral administration (10)

DMP can be absorbed after inhalation.

Distribution of DSM

After oral administration, DMP escaping metabolism in the gut epithelium and the liver, will distribute over all organs, including brain and fatty tissue(10) This is confirmed by human accident data in which deep coma was the most striking effect. Accumulation is not expected since over 95% of an oral dose is excreted within 24 hours (10)

Metabolism of DMP

Literature data indicate that up to 80% of DMP, absorbed from the gut, is readily attacked by esterases in the gut epithelium. The main metabolites in urine is mainly monomethylphthalate (and some phthalate), which are excreted in urine.(11) The remaining DMP is distributed over all body organs with initially a preference for liver and brain tissue. The liver also metabolises DMP through monoesterases. The other metabolite is initially methanol (later formaldehyde). In vitro experiments with radio-labeled DMP indicate that the carboxylic moiety can bind to intracellular macromolecules but not to nucleic acids. The formed formaldehyde is capable of binding to nucleic acids.(12)

After IP injection or in vitro, DMP is known to influence cholesterol and lipid metabolism, (10), to increase the amount of P-450 isoenzymes in the liver, and to decrease the activity of various other enzyme systems. (13,14)

B. Peroxidic compounds

Although the peroxides are unstable in water, they are probably sufficiently long-lived to reach the liver. In the 28 -day oral study, low-grade effects on the liver were observed, notably cytoplasmatic vacuolation of the periportal hepatocytes.(Notox report 338671) Liver damage was also reported in rats chronically given MEKP, an analogous ketoperoxide.(15) This finding is also in line with an observation in man where accidental intake of a large amount DMP containing around 45% MEKP was described. Severe periportal liver necrosis was seen in this patient, possibly due to induction of lipid peroxidation (16). The minor peroxidic compound is much less soluble in water and might be distributed into fatty tissue. However it is not expected to be very stable, ultimately also forming methyl isopropylketone (3-methyl-2-butanone). Since ketones are relatively easily metabolised, accumulation of these compounds is not expected.

Absorption through the skin is possible, especially of the type IV peroxide., although at the concentration as in the notified mixture severe corrosion will occur and part of the peroxides may react to extinction with the cells and cell debris. The nature of such reaction products is unknown. It is possible that peroxidic compounds absorbed through the skin and thus escaping first pass through the liver may get involved in lipid peroxidation of red blood cell membranes and thus cause hemolysis as has been described for the lower molecular weight analogon MEKP.

Significant distribution into brain and fatty tissue of any absorbed peroxidic compounds is deemed unlikely, given their reactivity and instability in water. Ketones formed in reaction with water may well distribute into brain and fatty tissue but are expected to be short-lived. Accumulation is not expected to occur.

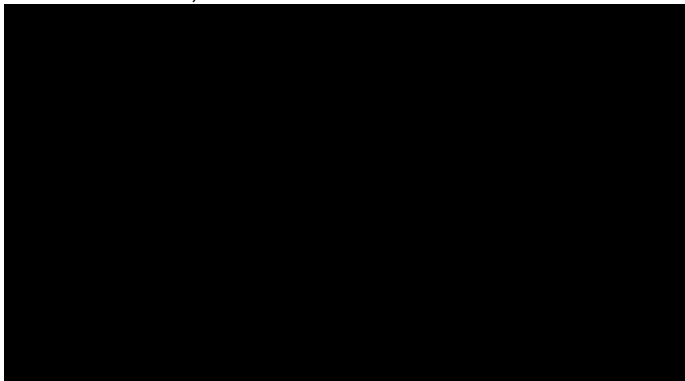
C Inhalatory exposure to the mixture.

Although the vapour pressure of the notified mixture is given as 761 Pa at 20° C (Notox report 338581) , this is probably due to the presence of water and methyl isopropylketone. According to literature data (17), DMP has a very low vapour pressure (3.08×10^{-3} mm Hg or 0.41 Pa at 25 deg C), and based on the molecular weight and structure, the vapour pressure of the peroxidic compounds should be of the same order of magnitude.

(the analogue MEKP or 2-Butanone peroxide is a mixture of dimers (50%), trimers (25%), and monomer peroxy compounds, If released to air, estimated vapor pressures ranging between 1.4×10^{-3} (0.19 Pa) and 2×10^{-3} mm Hg (0.27 Pa) at 25 deg C. The notified mixture contains mono- and dimers of MIPKP with a greater molecular weight than their equivalents in MEKP, therefore the vapour pressure should not exceed the higher value of 2×10^{-3} mmHg (0.27 Pa))

Therefore, inhalatory exposure is only of concern if exposure would occur in the form of an aerosol. In that case, severe local effects on mucous membranes may be expected, Absorption of DMP and of the peroxidic compounds and their breakdown products can be expected. However, since spraying of this preparation would serve no useful purpose and is therefore an unlikely source of exposure, this aspect is not further pursued.

Amersfoort, 03 March 2004



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